Overview and Integration of Cellular Metabolism

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Lecture 58: Fatty Liver and alcohol metabolism

Hello everyone, welcome back. We are at the last week of our lecture series for Overview and Integration of Cellular Metabolism. In today's class we are going to discuss two topics one is alcohol metabolism and disease condition related to it and many other is fatty liver. So, the concepts covered in this class will be related to alcohol metabolism. We will learn how metabolism of alcohol occurs in liver and what are their associated enzymes which help in metabolizing alcohol. Then of course, the toxic effect of alcohol how those toxic effects are imparted we will learn.

Then we will move on to fatty liver the different causes of fatty liver the basic biochemical platform which is actually causing fatty liver then of course, they are metabolic roles what what will be the consequences of fatty liver. So, let us move on to the very first alcohol metabolism. Now, metabolism of alcohol starts just after ingestion remember for the absorption alcohol is a molecule is a small molecule ethanol mainly is a small molecule then it is water soluble as well as lipid soluble. So, very fast it is absorbed from oral cavity to stomach to small intestine the major region major part is small intestine, but in stomach also in the gastric mucosa because you know there is very huge blood supply in the gastric mucosa as well as the intestinal mucosa there is fast passive absorption of alcohol.

Now, this absorption basically depends on many other factors starting from parsnalic factor to the substrate which is consumed there are different factors which actually decides the rate and extent of alcohol absorption. Like concentration of the alcohol which is consumed as well as the type of alcoholic beverage then regarding the person who is consuming alcohol their individual factors like age, gender, body weight, their metabolic capability, capacity then also whether they are fed or not based on that the rate and how much alcohol will be absorbed are decided. Then definitely after absorption when it enters in the blood stream it is distributed very fast and the peak blood alcohol concentration which is known as BAC it is obtained within 30 to 90 minutes it is very fast peak alcohol concentration is achieved after consumption that too also dependent on

those factors I already have mentioned. Now, because it is highly water soluble in from blood it enters the cells they alcohol freely diffuses across the cell membranes and is distributed to all the cells where there is water and present easily distributed inside the cell. Now, based on that multiple organs are affected by alcohol because alcohol can enter very easily important organs are brain, liver, heart, kidney, lungs even skeletal muscles.

Now, regarding brain because alcohol can cause can cross blood brain barrier very easily because of its molecular size which is very small as well as it is lipophilic. So, it can impart it effects over brain like cognitive function which is hampered then dementia these are the things which are hampered when alcohol reaches CNS in different concentrations. Then there are factors which decides the distributions like how the organ is perfused. So, the blood flow to the organ decides how much alcohol will enter and how we it will be distributed then again the concentration of the alcohol in the blood and also the rate of metabolism remember after entering the tissue alcohol is metabolized. So, how fast it is cleared from the system is also determining the effects of alcohol in body.

Now, remember regarding the clearance of alcohol liver is the most important organ. So, let us move on to metabolism of alcohol in liver. So, this is the major organ where alcohol is metabolized liver where there is the enzyme alcohol dehydrogenase. So, what happens basically alcohol is converted to aldehyde it is acetaldehyde and this alcohol dehydrogenase enzyme is present in cytosol. Now, remember one very important thing when there is conversion of alcohol or ethanol to acetaldehyde there is conversion of NAD to NADH.

So, basically this is one oxidation reaction. Now what is formed is acetaldehyde which is the actual toxic metabolite of alcohol. So, it is not ethanol or the end metabolite rather acetaldehyde which imparts the main toxic effect of alcohol. Now, 90 percent of these acetaldehyde is basically taken care of by liver and the enzyme is acetaldehyde dehydrogenase both of them are dehydrogenous. So, definitely both of them are actually using NAD which is converted to NADH, but importantly one thing to remember these NAD is cytosolic the NAD which is utilized by alcohol dehydrogenase is cytosolic whereas, the NAD which is utilized by acetaldehyde dehydrogenase that is mitochondrial enzyme.

Now, what is formed by acetaldehyde dehydrogenase is acetate which is a non toxic product. So, what is the fate of this acetate? Acetate which is formed in liver it can be activated to acetyl coenzyme A and the enzyme is acetyl coenzyme A synthetase the major isoform is isoform 1 acetyl coenzyme A synthetase 1 again that is 1 cytosolic

enzyme. Now, if you remember from the previous classes the fates of acetyl coenzyme A then you will be able to memorize that the cytosolic acetyl coenzyme A is basically utilized for biosynthesis biosynthesis of cholesterol fatty acids like that. Now, this acetyl coenzyme A which is formed in liver can enter liver mitochondria to undergo TCA cycle, but the commonest utilization of acetate is basically acetate is circulated through blood enters different organs like skeletal muscle heart and there it is getting converted to acetyl coenzyme A as and utilized as fuel for those organs. So, what happens the commonest sites are heart or skeletal muscle where there is once again acetyl coenzyme A synthetase isoform 2 which is the mitoch mitochondrial isoform.

So, in mitochondria once again acetate is converted to acetyl coenzyme A here you can see inside muscle converted to acetyl coenzyme A and it takes part in TCA cycle to form to give ATP or produce energy. So, this is the total metabolism of alcohol in liver the enzymes here important is first one is alcohol dehydrogenase. Now, this alcohol dehydrogenase there are different types of isoenzyme based on what type of alcohol it is. So, basically the alcohol the isoforms of alcohol dehydrogenase they are specific to the chain length of the alcohol, but for ethanol ethanol is a very small molecule and it has no diverse characteristics. So, what happens most I mean major it all of the alcohol dehydrogenase all of the isoforms can metabolize ethanol, but the highest the for the highest specificity of the isoform which is very much specific for ethanol is the class 1 alcohol dehydrogenase.

Now, you can see there are 5 classes of alcohol dehydrogenase amongst them there is class 1 which is more specific or very much active for metabolizing alcohol dehydrogenase and abundantly present in liver and also adrenal glands. Now, there are 3 genes for this alcohol dehydrogenase and then they together form polymorphic pattern. So, there are different alleles of alcohol dehydrogenase which renders polymorphism. So, this is about alcohol dehydrogenase, but for aldehyde dehydrogenase in the liver the major acetaldehyde dehydrogenase which is present in liver mitochondria is of isoform 2. So, mitochondrial acetaldehyde dehydrogenase is 2 that is also present in heart and skeletal muscle.

So, what the mitochondrial isoform is basically aldehyde dehydrogenase isoform 2 whereas, the cytosolic isoform is aldehyde dehydrogenase 1. Now, apart from this system ethanol the can be oxidized instead of alcohol dehydrogenase ethanol can be oxidized by another system which is known as Mieus, microsomal ethanol oxidizing system. So, definitely the enzyme is basically located in microsome or endoplasmic reticulum. Now, this Mieus or microsomal ethanol oxidizing system is basically a part of cytochrome P450 super family and there are multiple enzymes which can take part in alcohol oxidation, but the most important one is cytochrome P 2 E 1 which is a mixed

function oxidase. Now, what is the typical characteristics of these Mieus system where ethanol is converted to acetaldehyde here one important thing is molecular oxygen and another important thing is NADPH it is not NADH it is NADPH which is NADPH and oxygen they are utilized as electron donor NADPH is utilized as electron donor and molecular oxygen is the oxidizing agent here.

So, this is the difference with alcohol dehydrogenase induced ethanol metabolism. Now, only 10 to 20 percent of this ethanol oxidation this type of ethanol oxidation occurs in moderate drinkers normally ethanol is converted to acetaldehyde via alcohol dehydrogenase in liver. Then we are coming to the toxic effects imparted by alcohol and how they are causing this toxic toxicity. So, alcohol metabolism alcohol toxicity can be of 2 types one is acute alcohol toxicity another is chronic alcohol toxicity. Now, acute alcohol toxicity the major reason is increased NADH NAD ratio as I told you that when alcohol is metabolized alcohol is converted to acetaldehyde there is NADH formation again acetaldehyde is converted to acetate there is again NADH formation.

So, what happens when there is increased amount of alcohol which is metabolized there there is huge amount of NADH form. Now, what happens when there is a stable metabolic status metabolic homeostasis in our body this NADH which is produced can be reoxidized to NAD plus actually this in electron transport chain in mitochondria. But when there is huge amount of alcohol intake which is actually overwhelming the oxidation capacity of those NADH it causes accumulation of NADH or unavailability of NAD plus that is the main reason of acute toxicity of ethanol metabolism. Now, you can see here that ethanol when converted to acetaldehyde cytosolic NADH is increased again acetaldehyde when it is converted to acetate mitochondrial NADH is also increased. Now, NADH has no rather very poor product inhibition over the enzyme.

So, the enzyme goes on and NADH keeps on accumulating. Now, what are the effects rendered by this increased NADH NAD ratio? Number 1 is fatty acid metabolism altered how it is altered? So, there is huge amount of NADH available in mitochondria. Now, what actually beta oxidation of fatty acid does it provides NADH and beta oxidation when it is required in our body? When there is enough energy is not available ATP is not available. So, basically glucose or carbohydrate is now not available. So, fatty acids needs to provide energy.

So, it there is beta oxidation and that beta oxidation actually provides NADH as well as FADH 2 which enters which those are the reducing equivalents which enter TCA cycle sorry which enters electron transport chain to form ATP. Now, because there is enough or adequate amount of NADH in mitochondria beta oxidation is not occurring rather inhibited. So, one very important enzyme which is inhibited by high NADH content in

cell is CPT 1 which is related to beta oxidation of fatty acid. Now, carnitine palmitoyl transfer is one if you remember this enzyme was responsible for transferring activated fatty acid from cytosol to mitochondrial matrix. So, basically what happens this enzyme is in inhibited by high NADH which causes decreased beta oxidation.

Now because there is decreased beta oxidation. So, actually there is accumulation of those activated fatty acids what is the fate of those activated fatty acids. So, what happens is this fatty acyl coenzyme A are basically entering reesterification to form triacyl glycerol and this fatty acyl coenzyme A combines with glycerol 3 phosphate. Now interestingly synthesis of glycerol 3 phosphate in the glycolysis pathway is also increased because you if you remember once again dihydroxyacetone phosphate while it is converted to glycerol 3 phosphate NADH is required. So, there is adequate or rather high amount of NADH available which is forming high amount of glycerol 3 phosphate.

So, there is fatty acyl coenzyme A which is accumulated there is adequate supply of glycerol 3 phosphate that is causing formation of triacyl glycerol. Now moreover this enzyme for esterification of fatty acyl coenzyme A is a endoclasmic reticulum located enzyme which can be easily induced by the concentration of alcohol. So, alcohol can itself can induce reesterification of fatty acid. Now these triacyl glycerol is actually incorporated in VLDL and VLDL circulates in the blood which causes hyperlipidemia. So, this is the reason of ethanol induced hyperlipidemia.

So, remember why ethanol is causing hyperlipidemia because beta oxidation is inhibited due to huge supply of huge formation of NADH those fatty acyl coenzyme A along with glycerol 3 phosphate undergoes reesterification to form triacyl glycerol and that triacyl glycerol finally, comes to circulation forming VLDL or very low density lipoprotein. Apart from that these VLDL or triacyl glycerol sorry the triacyl glycerol as well as VLDL when it enters liver it also provides triacyl glycerol to the liver causing accumulation of triacyl glycerol finally, in the hepatocytes causing hepatic steatosis which means accumulation of liver and that is also known as fatty liver which we are going to discuss next. Then this fatty acids not only they are the effect of the this accumulation of fatty acid is not only the effect of inhibited beta oxidation rather there is increased lipolysis also because on ethanol consumption there is release of epinephrine and if you remember once again epinephrine is the hormone which activates hormone sensitive lipase. Hormone sensitive lipase acts on adipose triacyl glycerols undergoes hydrolysis to release fatty acids in circulation. So, again there is increased influx of fatty acids from lipolysis as well.

Also alcohol induces ketoacidosis there is excess amount of ketone body formation why again you can see acetyl coenzyme if you remember once again acetyl coenzyme is the

precursor of ketone body formation. Now, there is accumulation of acetyl coenzyme why? Number 1 because there is adequate availability of NADH which causes malate formation. So, basically oxaloacetate is actually forming malate. So, oxaloacetate is depleted now because oxaloacetate is forming malate acetyl coenzyme is not able to react with acetyl oxaloacetate to form citrate. So, basically acetyl coenzyme is not able to enter TCA cycle.

So, what will be the fate of those acetyl coenzyme? It is diverted to form ketone bodies excess amount of ketone body is formed. So, that is causing accumulation of ketone body. Moreover in circulation ketone body concentration we found in very high amount why? You remember there are few organs which can utilize ketone body as their fuel, but the problem is there is supply of acetate as well. So, acetate actually entering heart skeletal muscles for production of acetyl coenzyme. So, already there are there is supply of acetyl coenzyme in the form of acetate to those organ which could have utilized these ketone bodies.

So, basically those ketone bodies are only formed, but they are not utilized. So, in blood we are getting very high amount of ketone body that is causing ketoacidosis. So, remember once again in alcohol induced ketoacidosis not only there is increased formation of ketone body, but there is decreased utilization of ketone body as well. So, this is about fatty acid oxidation defects caused by ethanol apart from that there are multiple other toxicities which can be imparted over cell like lactic acidosis. Once again that is the cause of increased NADH NAD ratio.

So, lactate is formed in huge amount because there is NADH supply. So, pyruvate is actually forming lactate pyruvate that could have formed glucose via neo glucogenesis is actually shifted towards formation of lactate causing accumulation of lactic acid lactic acidosis. Now, these accumulated lactate has effect over uric acid excretion also. So, that is causing hyperuricemia the accumulated lactate actually decreases the excretion of uric acid by kidney. So, remember this point it often is asked why the patients with gout are advised not to drink excessive amount of alcohol.

So, gout is the condition which is already characterized by increased uric acid formation there is increased uric acid already in our body. Now, if those uric acids are not able to be excreted they these uric acids causes precipitation in different regions starting from joints to different kidney like that. So, gout is the condition which can be aggravated if patients take excessive amount of alcohol. Then hypoglycemia now remember this is very interesting patients the persons individuals who are on chronic alcoholism a very frequent drinker they often forget to take meals. For those patients hypoglycemia is a very predominant condition why because remember when the person is not taking meal

basically their energy supply is dependent on neoglucogenesis.

Now, one very important precursor of neoglucogenesis is pyruvate and amino acids like alanine or lactate itself they are the neoglucogenetic materials there. Now, due to availability of high amount of NADH lactate is not able to convert it to pyruvate rather it is happening the opposite just the opposite pyruvates are actually converted to lactate. Moreover those pyruvate which are formed from alanine or other neoglucogenetic precursors they are also forming lactate. So, basically these pathway is actually inhibited and the pyruvate is actually shifted to lactate formation. Moreover again if you remember oxaloacetate which is present in TCA cycle those oxaloacetates are also depleted because oxaloacetates are converted to malate just in the previous slide I told because there is availability of NADH in mitochondria oxaloacetates are basically converted to malate.

So, the neoglucogenesis is actually hampered. So, the person is going into hypoglycemia, but interestingly if a person takes ethanol along with a meal there is transient hyperglycemia hypoglycemia when there is decrease of blood glucose level hyperglycemia is when there is increase of blood glucose level. Now, when a person takes alcohol with meal there is hyperglycemia though that is a very transient situation now why it is there. Again if you remember this step that high NADH actually inhibiting glyceraldehyde 3 phosphate dehydrogenase. So, even if glyceral 3 phosphate is formed glyceraldehyde 3 phosphate dehydrogenase enzyme is not able to act.

So, the TCA cycle is hampered. So, basically glucose is not getting utilized. So, there is transient hyperglycemia in those patient those persons who are taking meal with alcohol, but that is once again is a transient condition remember this is a transient condition. So, we have discussed how the acute toxicity occurs from alcohol. Now, we are coming to chronic ethanol toxicity. Chronic ethanol toxicity is mostly the effect of acetaldehyde the intermediate and also free radicals which are generated during alcohol metabolism.

Now, the effect of chronic alcoholism are manifested in 3 different forms fatty liver alcohol induced hepatitis and cirrhosis. So, fatty liver is the accumulation of lipid in liver which when undergoes inflammation is causing hepatitis and then finally, there is fibrosis and tissue damage in liver which is causing cirrhosis. So, these are the chronic effect of alcohols over our body. Now, remember I am talking about chronic alcoholism. So, the individual is basically taking alcohol very frequently in very high dose for prolonged period.

So, apart from the effect of acetaldehyde itself there is formation of different adducts. So, acetaldehyde which is very highly reactive forms adducts with different amino

groups, sulfhydryl groups, nucleotides as well as phospholipids. So, this acetaldehyde adducts are able to impart some toxic effects in our body on chronic accumulation. Now, acetaldehyde how it causes alcohol induced hepatitis? Generally, acetaldehyde is causing a generalized hepatic protein synthesis decrease proteins like calmodulin, ribonuclease, tubulin these are the very common proteins which their synthesis are hampered. Now, tubulin is one such protein which causes assembly and secretion of VLDL.

So, basically there is diminished formation of VLDL. So, what will be the effect? Triacylglycerols which were coming to liver they are not getting secreted in the circulation rather accumulated in liver causing fatty liver. Apart from that there are multiple other proteins their synthesis are also hampered like serum albumin coagulation factor. Remember liver is the actually it is the synthetic hub in our body which is the main site of protein synthesis.

So, all the proteins their synthesis are hampered. Namely albumin coagulation factor different transport proteins which are actually transferring vitamins steroids, irons to different organs those proteins are accumulated they are not able to secreted even they are also forming adducts with lipid. So, what happens on these accumulation of protein there is influx of water in hepatocytes causing swelling of the liver which is finally, causing portal hypertension and finally, it is disrupting the whole hepatic cellular architecture. So, this is how alcohol induced hepatitis occurs via acetaldehyde. Next acetaldehyde adducts they are also able to impart injury via formation of free radicals. How you remember glutathione is one very important compound which is responsible for scavenging free radicals in our body.

Now acetaldehyde adducts they actually inhibits the glutathione function. Also mitochondria which is one hub for dealing with the free radicals its function is also hampered. Function in terms of rate of electron transport hampered, oxidative phosphorylation is hampered, uncoupling of oxidative phosphorylation causing heat release. So, these are the effects over mitochondria. Now, again fatty acid oxidation it occurs inside mitochondria.

So, whenever there is mitochondrial function hampered fatty acid oxidation will also be hampered it will cause more lipid accumulation. So, basically these toxicities occurring in a cycle those fatty acid adducts with lipid they are hampering the mitochondrial function. Mitochondrial function then hampering the beta oxidation of fatty acid causing more accumulation of lipid those lipids are once again forming adduct with acetaldehyde. So, this is a progressive cycle of damage due to free radical formation. Then one very important enzyme here cytochrome P 2 E 1 which is important in a MEO system for metabolizing alcohol.

This is one very important site of free radical formation. Enzymes which contain FMN, FAD in reductase, flavin adenine dinucleotide, flavin mononucleotide or present in reductase or in heme of cytochrome P450 system they actually transfer single electrons and they are the very soft targets where free radical is formed. Now, one such free radical is hydroxy ethyl radical which is accumulated during chronic ethanol abuse. So, basically these enzymes are actually induced by alcohol to form more because these enzymes remember my these are the microsomal enzymes and microsomal enzymes are very much inducible by the substrate. So, whenever there is increased amount of substrate alcohol it those enzymes are their activity is actually increased and because their activity is increased the free radical generation is also increased. Now, one very important target of free radical induced damage is phospholipids which are present in membrane.

Now, just imagine mitochondrial membrane is basically the affected by the lipid peroxides the free radicals formed during alcohol metabolism. Now, this on this lipid peroxidation enzymes which are present over mitochondria or the electron transport chain that will be hampered as well as if there is leakage in mitochondrial membrane there will be uncoupling of the whole electron transport chain finally, causing an energy disbalance as well as tissue damage. Also there are different types of carcinogens. Carcinogens are those products which can cause cancer in our body. So, but they remain in inactive form there should be some trigger which activates this carcinogens.

So, free radicals are such triggers which can activate carcinogens in liver causing hepatocellular carcinoma. So, this is one cause of hepatocellular carcinoma induced by alcohol chronic alcoholism. So, now we are coming to our next topic that is fatty liver the spectrum is also known as fatty liver disease or hepatitis T r to C's. Now, fatty liver is basically the accumulation of lipid in liver, but remember liver is the site of lipid biosynthesis. In a well fed person these are the metabolic steps related to lipid metabolism which occurs in liver like de novo synthesis of fatty acids, triacylglycerol synthesis, cholesterol synthesis, phospholipid synthesis, glycolipid biosynthesis, VLDL biosynthesis all these metabolism or biosynthesis of lipid molecule actually occurs in liver, but liver is not the organ which stores lipid.

Normally less than 5 percent 3 to 5 percent only lipids are present in hepatocytes majority of the lipids which are actually synthesized in liver they are released in the circulation in the form of VLDL. Now, the problem is if there is increased supply of lipid production of lipid or supply of lipid in liver which cannot be at pace with its secretion in the form of VLDL or the supply of lipid is ok, but there is some problem with VLDL formation this condition can lead to accumulation of lipid in liver causing fatty liver. So,

basically fatty liver is steatosis where more than 5 percent of lipid is actually retained in hepatocyte. Now remember fatty liver disease is basically a reversible condition large vacuums of lipid accumulates in liver, but if it undergoes if it remains for long standing for long duration it can have inflammation. So, this progressive inflammation over steatosis is actually causing steatohepatitis.

What will be the consequences of this there will be non alcoholic fatty liver disease remember alcohol can cause the spectrum of fatty liver disease, but there are other triggers apart from alcohol that also can cause fatty liver or the spectrum. So, that can be non alcoholic fatty liver disease, non alcoholic steatohepatitis, cirrhosis, hepatocellular carcinoma finally, liver failure the whole organization of liver functions are hampered causing liver failure starting from synthetic synthesis to excretion everything. So, what are the metabolic defect actually which is finally, developing fatty liver. So, number 1 is if there is sorry the main point of the fatty liver formation is definitely there is an imbalance between supply and mobilization. So, supply in the form of endogenous triacylglycerol formation and mobilization in the form of VLDL formation.

So, whatever triacylglycerol is actually formed or reach reaches liver those are released via VLDL instead of accumulating, but if these balance is hampered there is accumulation. Now what are the causes which can cause triacylglycerol formation defect if there is increased flux of fatty acid in liver or if the diet which can form increase for increase free fatty acid in liver there will be huge amount of triacylglycerol or substrate supply. Again if the transfer triacylglycerol formation is fine by that, but their mobilization or release in the form of VLDL is defective that can cause fatty liver like defective apoprotein synthesis. Remember apoprotein is one very important protein part for lipoprotein formation the lipid which is assembled in lipoprotein their synthesis can be hampered. Synthesis of apoprotein and lipid are fine, but their assembly is defective.

Then finally, the assembly is ok, but the formed VLDL is not able to be secreted. So, these are the defects which can lead to fatty liver. Let us see more in details. So, what are the increased cause of free fatty acid influx? If there is increased lipolysis from adipose tissue that can cause increased free fatty acid flux. The condition can be uncontrolled diabetes mellitus or prolonged starvation when where there is increased lipolysis which I have already discussed in integration of metabolism.

Then diets which contain very high fat or high carbohydrate. Carbohydrate can form fat in liver and those can be the influx for TAG or triacylglycine formation. Then defects in VLDL formation apoprotein synthesis can be defective. Now there are multiple drugs which inhibits protein synthesis like puromycin, ethionine. Now ethionine you if you hear this it is quite resembling with methionine. So, basically it is actually causing some

problem in methionine metabolism.

What is the problem? Remember when there is this ethionine is have some structural resemblance with methionine. So, instead of methionine while there is S-adenosyl methionine formation S-adenosyl methionine formation ethionine can be incorporated instead of methionine. Now what happens adenosyl group which has adenine it is basically blocked because finally, when there is ethionine instead of methionine that cannot take part in methyl transfer reaction. So, basically adenine is trapped. Now when there is adenine trapped there is definitely some problem in ATP formation.

So, basically that is causing energy deficient status which is induced by ethionine. Again CCL 4 chloroform lead these are the molecules which inhibits protein synthesis as well as a generalized malnutrition protein energy malnutrition that can also cause decreased protein availability on synthesis which actually causes apoprotein synthesis. It causes ham I mean defective apoprotein synthesis which is finally, reflected in VLDL formation. Then there is defective lipid synthesis. So, phospholipid synthesis can be hampered because there are different molecules which are responsible for phospholipid synthesis those are known as lipotropic factors.

So, if there is deficiency of lipotropic factors or defect in lipotropic factor they can cause defective lipid synthesis which is reflected in VLDL formation defect. Then the assembly of VLDL can also be defective. Remember if there is damage in hepatocytes like hepatitis alcohol induced hepatitis or some drug induced hepatitis viral hepatitis infective or inflammatory conditions. If the cell which is actually causing the assembly hepatocyte is damaged the ultimate formation of lipoprotein will be hampered. Then secretory defect in VLDL now orotic acid is one such molecule which causes secretory defect in VLDL.

Actually VLDL undergoes glycosylation for its secretion. Now orotic acid inhibits this glycosylation on VLDL. So, VLDL ultimately which is formed is only residing in liver is not able to be secreted in the circulation. So, these are the conditions where mobilization of fat is hampered in fatty liver. Now one very important term I have told that is lipotropic factors which is that can be defined as the substances which help in formation of phospholipid. And because they help in formation of phospholipid they are very important in mobilization of VLDL from liver.

Now what are the molecules or what are the lipotropic factors? Now if you remember from the phospholipid synthesis class choline, methionine, serine these are the molecules which are important for synthesizing phospholipid. Choline for lecithin phosphatidylcholine. Methionine is the methyl group donor S adenosyl methionine to

form phospholipid. Again phosphatidyl serine is also one very important phospholipid.

So, these are if these are deficient adequate phospholipid cannot be formed. Then essential fatty acids like linoleic acid they are the part of phospholipid, then vitamin E and selenium. Now these are the molecules which are important for free radical scavenging. So, free radical induced damage causes phospholipid formation defect. So, these are the lipotropic factors which are important for phospholipid formation and their deficiency can cause defective VLDL formation. So, finally, fatty liver remember this is the imbalance between the triacylglycil formation and its mobilization.

So, let us learn the key points of this session. We have discussed alcohol metabolism. The major site of alcohol metabolism is in is liver where hepatic alcohol dehydrogenous which is the cytosolic enzyme and acetaldehyde dehydrogenous which is the mitochondrial enzyme they are the most important enzymes. Now the toxic intermediate of alcohol metabolism is acetaldehyde. Apart from this system there is meos, microsomal oxidizing system which is responsible for 10 to 20 percent of ingested ethanol metabolism and the acute alcohol toxicity we have discussed that is where the main reason of acute toxicity is basically increased NADH NAD ratio in liver. And finally, the next topic fatty liver is where we have discussed regarding the pathogenesis how the imbalance of influx of lipid and clearance are actually causing fatty liver and also discuss lipotropic factors. These are my references. Thank you all.